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Task 3. Analogs of Tetrahydrocannabinol
for
Chemical Corps Procurement Agency

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Progress Report
from

February thru March, 1959

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SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

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Bi-Monthly Report No. 4

on

TASK 3

for

Chemical Corps Procurement Agency

under

Contract No. DA18-108-CML-4564

Period Covered: February through March 1953

Written by: D. E. Winkler

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CONTENTS

Summary	page 1
Analogs of Tetrahydrocannabinol	1
Changes in Alkyl Groups	1
Nitrogen and Sulfur Analog	2
Appendix	3

S-13460

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Summary

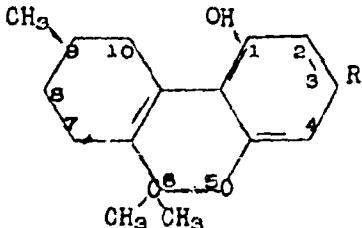
One of the most active tetrahydrocannabinol analogs mentioned by Adams^{a)} (Formula I, R=2-nonyl) has been completed. The preparation of the second of Adams' compounds (R=1,2-dimethylheptyl) is now at the stage of 2(3,5-dimethoxyphenyl)-3-methyloctene-2 and requires four more steps.^{b)}

The preparation of nitrogen and sulfur analogs is being approached by two different methods which were suggested in the previous report.^{c)} One starting with 3,5-dinitrobenzoic acid has been carried through five steps to 3-methoxy-5-chlorobenzoic acid. The second method which involves the preparation of 3-amino-5-hydroxy n-amyl benzene from the corresponding dihydroxy compound has been shown to be feasible. The preparation of 3,5-dihydroxy n-amyl benzene from 3,5-dimethoxyphenyl butyl ketone has presented unexpected difficulties.

Analogs of Tetrahydrocannabinol

Changes in Alkyl Groups

The structure of tetrahydrocannabinol (I, R=n-C₅H₁₁) is given again for reference:



I

The steps leading to Adams' two most active tetrahydrocannabinol analogs have been described in a previous report.^{c)} The synthesis of one of these compounds, 1-hydroxy-3-secondary nonyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (I, R=2-nonyl) has been completed and the last two steps are described in the Appendix.

The preparation of the second of Adams' compounds in which the alkyl group (R in Formula I) is 1,2-dimethylheptyl has been carried through to 2(3,5-dimethoxyphenyl)-3-methyloctene-2. Four steps remain, i.e., reduction splitting of the methyl ethers, condensation with ethyl 5-methylcyclohexanone-2-carboxylate to form the pyrone followed by reaction with methyl magnesium iodide.

a) Adams, R., MacKenzie, S., and Loewe, S., J Am Chem Soc, 70 664 (1948).
b) Winkler, D. E., Progress Report 2 (1952).
c) Winkler, D. E., Progress Report 3 (1953).

S-13460

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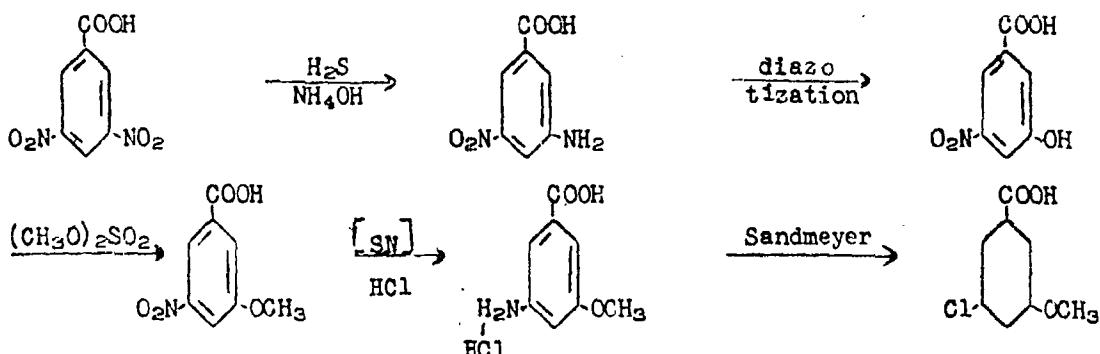
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-2-

Nitrogen and Sulfur Analogs

The preparation of nitrogen and sulfur analogs of tetrahydrocannabinol is being approached by two methods which were outlined in a previous report.^{a)} The method which starts with 3,5-dinitrobenzoic acid has been carried through the following five steps to 3-methoxy-5-chlorobenzoic acid:



A description of three of these steps is given in the Appendix.

The second proposed route for preparing the nitrogen or sulfur analogs involves the reaction of ammonia with 3,5-dihydroxy amylbenzene to produce 3-amino-5-hydroxy amylbenzene. This reaction has been found to go on a small scale and should not present any problem for it has been shown that 3-amino-5-hydroxy toluene can be produced in 82% yield from 3,5-dihydroxy toluene by following the directions of Bean and Donovan,^{b)} for resorcinol, which involves heating the dihydroxy compound with aqueous ammonia and di-ammonium phosphate for twelve hours at 200°C. Considerable difficulty is being experienced in the preparation of 3,5-dihydroxy amylbenzene from 3,5-dimethoxyphenyl butyl ketone. This ketone can be prepared from 3,5-dimethoxy benzamide and butyl magnesium bromide.^{c)} Two steps are required in going from the above ketone to the desired resorcinol derivative, i.e., reduction of the carbonyl group to the hydrocarbon and splitting of the methyl ethers. Catalytic hydrogenolysis and three variations of the Elemmenson method have been tried with only a small degree of success. The Huang-Minlon^{d)} modification of the Wolff-Kishner method is being tried and preliminary results indicate a yield of 78%.

a) Winkler, D. E., Progress Report 3 (1953).

b) Bean, F. R., and Donovan, T. S., (to Eastman Kodak Co.), U.S. Patent 2,376,112 (1942).

c) Winkler, D. E., Progress Report 2 (1952).

d) Huang-Minlon, J Am Chem Soc, 68 2487 (1946).

S-13460

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-3-

APPENDIX

1-Hydroxy-3-Secondary Nonyl-9-Methyl-7,8,9,10-Tetrahydro-6-Dibenzopyrone, $C_{23}H_{32}O_3$	page 1
1-Hydroxy-3-Secondary Nonyl-6,6,9-Trimethyl-7,8,9,10-Tetrahydro-6-Dibenzo- pyran, $C_{25}H_{38}O_2$	2
3-Amino-5-Nitrobenzoic Acid, $C_7H_6O_4N_2$	3
3-Hydroxy-5-Nitrobenzoic Acid, $C_7H_5O_5N$	4
3-Methoxy-5-Nitrobenzoic Acid, $C_8H_7O_5N$	5

S-13460

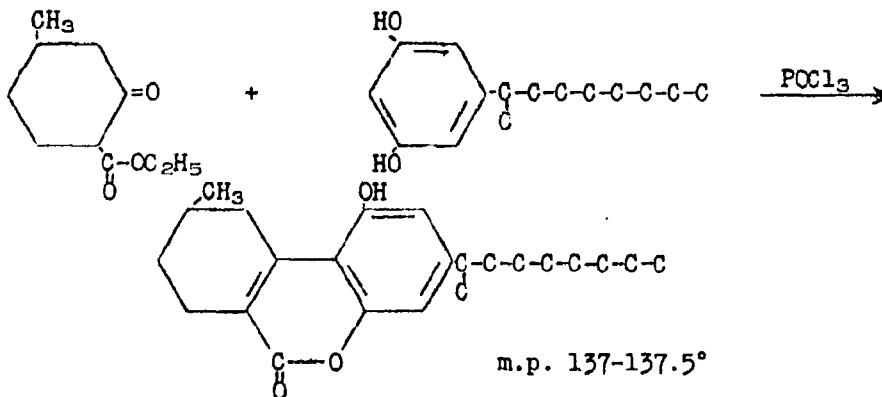
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-1-

1-Hydroxy-3-Secondary Nonyl-9-Methyl-7,8,9,10-Tetrahydro-6-Dibenzopyrone,
C₂₃H₃₂O₃



Ethyl 5-methylcyclohexanone-2-carboxylate (0.418 mols, 76.8g), 2-(3,5-dihydroxyphenyl) nonane (0.418 mols, 98g), phosphorus oxychloride (0.418 mols, 64g), and 500 cc of anhydrous benzene were charged to a kettle and heated slowly to refluxing temperature. At 60°C HCl started to come off. Refluxing was continued for two hours at 80°C. The product was cooled, washed with water, dilute sodium bicarbonate solution and again with water. Benzene was flashed off under vacuum and the product recrystallized twice from ethyl acetate. A 68% yield of purified product was recovered which melted at 137-137.5°C on an aluminum block. Adams^{a)} reports 138°C.

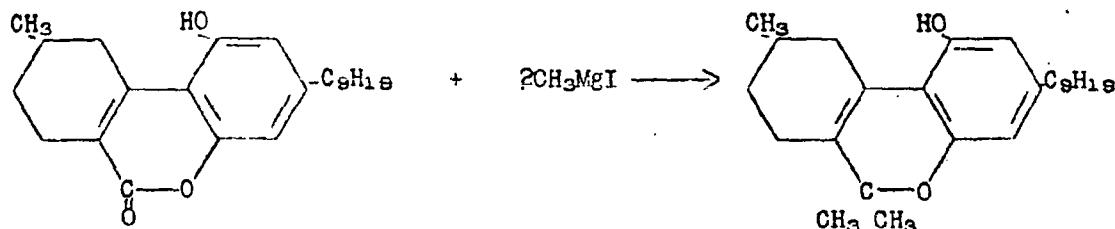
Analyses calcd for C₂₃H₃₂O₃: C, 77.4; H, 9.06
Found: C, 77.1; H, 8.9

a) Adams, R., Aycock, B. F., and Loewe, S., J Am Chem Soc, 70 662 (1948).
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1-Hydroxy-3-Secondary Nonyl-6,6,9-Trimethyl-7,8,9,10-Tetrahydro-6-Dibenzopyran,
C₂₅H₃₈O₂



b p 205-10°/.01 mm

A solution of 91g (0.255 mol) of 1-hydroxy-3-secondary nonyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone in 2300 ml of anhydrous benzene was added over a period of fifty minutes to a refluxing Grignard solution prepared from magnesium (76g, 3.12 mol) and methyl iodide (468g, 3.3 mol) in 1000 ml of ether. After the pyrone was added, ether was boiled off to a kettle temperature of 75°C and refluxing continued for twelve hours. The product was cooled and 1000g of 20% ammonium chloride solution added. The oil layer was washed with water, 5% sodium bicarbonate solution, and again with water. After removing the solvent, 84g (89% yield) of product were recovered boiling 205-210°C at ca. 0.01 mm.

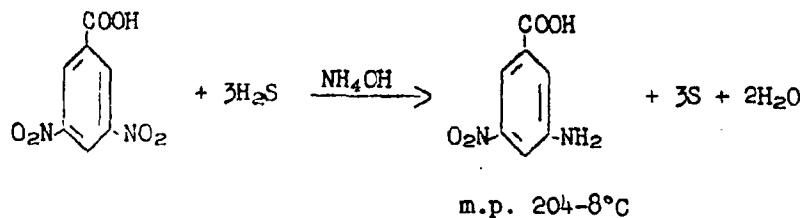
Analyses calcd for C₂₅H₃₈O₂: C, 81.0; H, 10.3
Found: C, 80.9; H, 10.3

S-13460

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-3-

3-Amino-5-Nitrobenzoic Acid, C₇H₆O₄N₂



To a stirred solution of 600 ml of ammonium hydroxide (sp. gr. 0.90), 1200 ml of water and 636g (3 mols) of 3,5-dinitrobenzoic acid kept at 90°C ± 5°C, there was added 362g (10.6 mols) of H₂S in a period of three to four hours. The solution was heated to boiling and a stream of natural gas bubbled through for twenty minutes. The solution was filtered while still warm to remove the sulfur and the 3-amino-5-nitrobenzoic acid was precipitated by adding 200g of acetic acid. After one crystallization from 1800 ml of water, 442g (81% yield) of product, mp 204-208°C with decomposition, was obtained. Hubner^{a)} reports a mp of 208°C with decomposition.

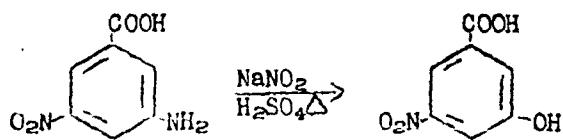
a) Hubner, H., Ber 10 1703 (1877).

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3-Hydroxy-5-Nitrobenzoic Acid, C₇H₅O₅N



mp 175-180°C (crude)

3-Amino-5-nitrobenzoic acid (216g, 1.19 mols) was added to a solution of 1050 ml of conc H₂SO₄ and 1050 ml of water. The mixture was warmed to 70°C to effect solution and then cooled to 0°C at which temperature 90g (1.3 mols) of solid sodium nitrite was added in about 30 minutes. The diazonium salt was decomposed by heating to 140°C over a period of about two hours. The product was diluted with one l of water, cooled to room temperature and extracted with 4-700 ml portions of ether. Evaporation of the ether left 203g of crude 3-hydroxy-5-nitrobenzoic acid mp 175-180°C. Since no suitable recrystallizing solvent was found the crude product was used in the next step without purification. Beyer^a) reports a melting point of 194-5°C after recrystallization from 25% hydrochloric acid.

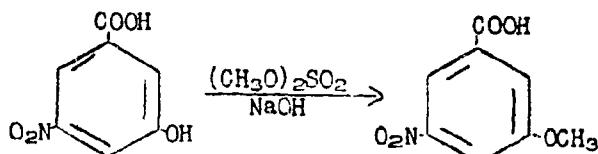
a) Beyer, Rec Trav Chim 40 625.

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-5-

3-Methoxy-5-Nitrobenzoic Acid, C₈H₇O₅N



mp 191-2°C

Crude 3-hydroxy-5-nitrobenzoic acid (335g, 1.83 mols) from the previous experiment was dissolved in a solution of 227g of sodium hydroxide in 1700 ml of water. While stirring and maintaining the temperature at 30-35°C, 504g (4.0 mols) of dimethyl sulfate was added dropwise. After refluxing two hours, 264g of 50% sodium hydroxide was added and the refluxing continued for two more hours. The reactants were diluted with 2 l of water and acidified with 600 ml of 6N HCl. After washing and drying the crude 3-methoxy-5-nitrobenzoic acid mp 162-8°C, weighed 325g. When purified by recrystallizing from water it melts 191-2°C. This is believed to be a new compound.

Analyses calcd for C₈H₇O₅N: C, 48.8; H, 3.6
Found: C, 49.0; H, 3.7

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